The University of Chicago

DERIVATIVES OF 4-METHYL-5-ETHYLURACIL

A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1937

By

JULIAN A. OTTO

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I. INTRODUCTION

For the last several years considerable work has been done in this laboratory on the preparation of 5,5-disubstituted ureides of the acetoacetic acid series. The work in this field was stimulated by the hope that these ureides would possess pharmacological activities similar to those possessed by the 5,5-disubstituted ureides of the malonic acid series. Even greater assurance for success in this work was gathered from the recent discovery[1] that the more closely related hydrouracils possess soporific qualities of the same order of effectiveness as the barbiturates.

Although all efforts applied towards the preparation of 5,5-disubstituted alkyl or aryl ureides of the acetoacetic acid series have met with failure, one of the workers[2] was able to prepare a compound having the composition of 4-methyl-5-dimethylamino-5-ethyluracil[3] by treating brominated 4-methyl-5-ethyluracil with dimethylamine. The molecular structure, however, of this dimethylamino compound as well as that of the brominated 4-methyl-5-ethyluracil remained unestablished. The proof of the structure of these two compounds is the chief concern of the present work. For these structural proofs the determination of the position of the bromine atom in the brominated 4-methyl-5-ethyluracil is of vital importance and for that reason will be

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[1] Merk, Chem. Abstr., 29, 1583 (1935).

[2] Metzner, Unpublished Work.

[3] The nomenclature used for uracil and its derivatives in this report corresponds to the nomenclature unanimously adopted by the other workers of this laboratory in the field of the uracils. It is the nomenclature used by Behrend and his co-workers (cf. later references). According to this uracil is 2,6-pyrimidinedione, for which the numbered formula is

1 2 3 4 5 6
NH.CO.NH.CH:CH.CO.

In the Chemical Abstracts uracil is considered as 2,4-pyrimidinedione, having the numbered formula

1 2 3 4 5 6
NH.CO.NH.CO.CH:CH.

given considerable attention. Once this position has been determined the number of the compounds that can be formed by the reaction of this brominated compound with dimethylamine is quite limited and for that reason the structure of the reaction product can be determined with greater facility.

II. DISCUSSION OF RESULTS

A. Bromination of 4-Methyl-5-Ethyluracil

The mono-brominated uracils recorded in the literature have been prepared by two distinct types of reactions. By one method the uracil is suspended in carbon disulfide and treated with dry bromine. The resulting reaction is tantamount to a direct substitution of a hydrogen atom by a bromine atom. By the other method the uracil is treated with bromine water. This reaction results in the formation of a monobromo- or dibromohydroxyhydrouracil which by the elimination of a molecule of water in the case of the monobromo compound or a molecule of hypobromous acid in the case of the dibromo compound, yields a mono-brominated uracil. Since both of these experimental procedures were used for the preparation of the brominated 4-methyl-5-ethyluracil here in question, they will be discussed separately in the following paragraphs. The discussion of the second method will be in two parts: first, the formation of the bromohydroxyhydrouracils and, second, the conversion of these bromohydroxyhydrouracils to mono-brominated uracils. A fourth topic to be discussed is the formation of a dibromohydroxy-4-methyl-5-ethylhydrouracil.

1. Direct Substitution. The method of direct substitution was successfully employed by Behrend[1] when he prepared 4-methyl-5-bromouracil by treating 4-methyluracil suspended in carbon disulfide with dry bromine:

$$\underline{NH.CO.NH.C(CH_3):CH.CO} + Br_2 \longrightarrow \underline{NH.CO.NH.C(CH_3):CBr.CO} + HBr$$

In a similar manner Wheeler and Merriam[2] were able to convert uracil into 5-bromouracil, $\underline{NH.CO.NH.CH:CBr.CO}$. It was this method that was used by Metzner[3] when he prepared a mono-brominated 4-methyl-5-ethyluracil from 4-methyl-5-ethyluracil. One's attention

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[1] Behrend, Ann., 231, 248 (1885).

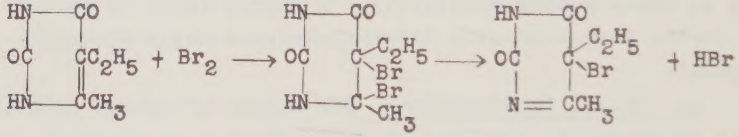
[2] Wheeler and Merriam, Am. Chem. Jour., 29, 486 (1903).

[3] Metzner, loc. cit.

is, of course, drawn to the fact that both uracil and 4-methyl-uracil have a replaceable hydrogen atom on the carbon atom in the 5-position of the uracil ring, whereas 4-methyl-5-ethyluracil, as ordinarily written, does not. There is, however, the possibility of a second tautomeric form that would permit direct substitution of a hydrogen atom by the bromine:

$$NH.CO.NH.C(CH_3):C(C_2H_5).CO \rightleftharpoons NH.CO.N:C(CH_3).CH(C_2H_5).CO$$

Nevertheless, it is quite doubtful that the monobromo compound is formed by the direct substitution of the hydrogen atom in the 5-position of the second form. One reason is that in the case of the second form the configuration around the 5-carbon atom is greatly similar to that of the 5-carbon atom of the hydrouracils, and the hydrouracils do not react readily with bromine—a temperature of 100° or more being required.[1] There is more reason to believe that the mono-brominated 4-methyl-5-ethyluracil is formed by the addition of bromine to the ethylene double bond between the 4- and 5-carbon atom with the subsequent splitting off of a molecule of hydrogen bromide as indicated by the following equations:



The fact that the addition product can be isolated when 4-methyl-5-ethyluracil is treated with hypobromous acid in place of dry bromine (a reaction to be discussed later in greater detail) argues in favor of the addition of bromine to the ethylene double bond. That this dibromo addition product cannot be isolated because it readily loses a molecule of hydrogen bromide need cause no great concern, for it is a well-known fact that the somewhat analogous amido- and imido-halides readily lose hydrogen halide.[2]

It may be of interest to point out at this point that there is a considerable difference in the behavior of ordinary

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[1] Fischer, Ber., 34, 3751 (1901).

[2] A. Bernthsen, Organic Chemistry (new and enl. ed.; New York: D. Van Nostrand Co., 1933), p. 192.

commercial bromine and chemically pure (C.P.) bromine towards 4-methyl-5-ethyluracil suspended in carbon disulide. Commercial bromine reacts rather vigorously when it is first added to the uracil and at the same time hydrogen halide fumes are evolved. On the other hand, when C.P. bromine is added to the uracil, there is neither a vigorous reaction nor any extensive evolution of hydrogen bromide. Various catalysts or bromine "carriers," such as iodine, chlorine, ferric bromide, aluminum chloride and a trace of moisture, were added to C.P. bromine to determine the cause of this difference in behavior. It was eventually found that the difference was due to a small amount of chlorine (about 0.5 per cent) that is present in commercial bromine as an impurity. When C.P. bromine was adulterated with about 0.5 per cent of chlorine and this mixture added to the 4-methyl-5-ethyl-uracil the behavior was similar to that observed when commercial bromine was added. Since in both cases bromination was incomplete after the first violent reaction had subsided, this decrease in reactivity was in all probability due to the exhaustion of the supply of chlorine. Chlorine, when added alone to the 4-methyl-5-ethyluracil suspended in carbon disulfide, reacts very vigorously and the reaction is accompanied with an abundant evolution of hydrogen chloride. The reaction does not stop with the formation of the monochloro 4-methyl-5-ethyluracil. A quantitative analysis indicated that a mixture of compounds containing from four to five chlorine atoms was formed when chlorine was added to the uracil till no further reaction could be observed. Attempts to prepare the monochloro compound failed. When the uracil was treated with an equimolar quantity of chlorine the product was a mixture of non-chlorinated and poly-chlorinated 4-methyl-5-ethyluracils.

Regarding the other halogen "carriers" or catalysts that were added to C.P. bromine, namely, iodine, ferric bromide, aluminum chloride and a trace of moisture, it may be pointed out here that the same product was formed in each case. Further details concerning the effects of these compounds will be given in the experimental part of this report.

2. Formation of Bromohydroxyhydrouracils. When uracils are treated with bromine water, or when bromine is added to uracils suspended in water, hypobromous acid is absorbed by the

uracils at the ethylene double bond with the result that bromohydroxyhydrouracils are formed. The uracils that have a replaceable hydrogen atom on the 5-carbon atom not only absorb hypobromous acid at the double bond but also have this hydrogen replaced by bromine. The resulting product is a dibromohydroxyhydrouracil. Thus 4-methyluracil reacts with bromine water to form 5,5-dibromo-4-hydroxy-4-methylhydrouracil.[1]

$$\underline{NH.CO.NH.C(CH_3):CH.CO} + 2Br_2 + H_2O \rightarrow \underline{NH.CO.NH.C(OH)(CH_3).CBr_2.CO} + 2HBr$$

The uracils not having a hydrogen atom on the 5-carbon atom simply absorb hypobromous acid at the ethylene double bond. Thus thymine, 5-methyluracil, absorbs hypobromous acid to form 4-hydroxy-5-bromo-5-methyluracil.[2]

$$\underline{NH.CO{\cdot}NH.CH:(CH_3).CO} + Br_2 + H_2O \rightarrow \underline{NH.CO.NH.CH(OH).CBr(CH_3).CO} + HBr$$

The major point of interest in the present problem is whether the bromine goes to the 4- or 5-carbon atom when hypobromous acid is absorbed at the ethylene double bond. As already indicated by the last two equations above, Behrend, in the case of 4-methyluracil, and Jones, in the case of 5-methyluracil, consider the bromine atom to go to the 5-carbon atom. The fact that dibromobarbituric acid is formed[3] when the dibromohydroxy 4-methyluracil is oxidized with red fuming nitric acid proves conclusively that in the case of 4-methyluracil the bromine atom of the hypobromous acid does go to the 5-carbon atom. Thus for the oxidation we have the equation:

$$\underline{NH.CO.NH.C(OH)(CH_3).CBr_2CO} + 4[O] \rightarrow \underline{NH.CO.NH.CO{\cdot}CBr_2CO} + CO_2 - 2H_2O$$

The bromine atom of hypobromous acid absorbed at the ethylene double bond has also been assigned to the 5-carbon atom by Behrend[4] in the case of 5-nitrouracil, by Hagen[5] in the case

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[1]Behrend, Ann., 229, 18 (1885).

[2]Jones, Z. physiol. Chem., 29, 20 (1900).

[3]Behrend, Ann., 236, 62 (1886).

[4]Ibid., 240, 1 (1887).

[5]Hagen, Ann., 353, 250 (1907).

of 1,3,4-trimethyluracil, and by Hoebel[1] in the case of 1-benzyl-4-methyluracil.

On the other hand, the bromine atom has been assigned to the 4-carbon atom by Bremer[2] in the case of 1,4,5-trimethyluracil and 1-phenyl-4,5-dimethyluracil,[3] and by Kircher[4] in the case of 4,5-dimethyluracil.

This last mentioned compound is of special interest because of the fact that it is so closely related to the uracil under consideration in this work; the only difference being that Kircher's compound has a methyl group on the 5-carbon atom instead of an ethyl group. This 4-methyl-5-ethyluracil also forms an addition product with hypobromous acid. If the assumption made by Kircher, that 4-bromo-5-hydroxy-4,5-dimethylhydrouracil is formed when 4,5-dimethyluracil is treated with hypobromous acid, is correct, then, one would have good reason to believe that when 4-methyl-5-ethyluracil is similarly treated the analogous 4-methyl-4-bromo-5-hydroxy-5-ethylhydrouracil should be formed. The following equations indicate that analogy very clearly:

$$\underline{NH.CO.NH.C(CH_3):C(CH_3).CO} + HOBr \rightarrow \underline{NH.CO.NH.CBr(CH_3).C(OH)(CH_3).CO}$$

$$\underline{NH.CO.NH.C(CH_3):C(C_2H_5).CO} + HOBr \rightarrow \underline{NH.CO.NH.CHr(CH_3).C(OH)(C_2H_5).CO}$$

However, Kircher does not prove conclusively the structure of his compound and furthermore, it is quite possible that 4,5-dimethyluracil and 4-methyl-5-ethyluracil do not react with hypobromous acid in a similar manner. In the present work it was found that 4-methyl-5-ethyluracil does not react in the manner indicated by the above equation. When the product of the reaction with hypobromous acid is oxidized with red fuming nitric acid, bromoethylbarbituric acid is formed. This indicates clearly that in the case of 4-methyl-5-ethyluracil the bromine atom of the hypobromous acid goes to the 5-carbon atom. The addition and oxidation reactions may, then, be expressed as follows:

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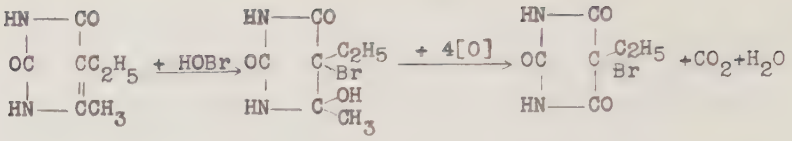
[1]Hoebel, Ann., 353, 265 (1907).

[2]Bremer, Ann., 378, 200 (1911).

[3]Ibid., p. 209.

[4]Kircher, Ann., 385, 307 (1911).



3. Conversion of Bromohydroxyhydrouracils to Monobrominated Uracils. Nearly all of the bromohydroxyhydrouracils when refluxed with absolute alcohol or heated by themselves lose either a molecule of hypobromous acid or a molecule of water and so become unsaturated compounds. Thus, when 5,5-dibromo-4-hydroxy-4-methylhydrouracil is refluxed with absolute alcohol 4-methyl-5-bromouracil is formed[1] and the alcohol is oxidized to an aldehyde.

$$\underline{NH.CO.NH.C(OH)(CH_3).CBr_2.CO} + C_2H_5OH \longrightarrow$$
$$\underline{NH.CO.NH.C(CH_3):CBr.CO} + C_2H_4O + H_2O + HBr$$

The product of this reaction will be recognized as the same compound that was formed by direct substitution when 4-methyluracil was treated with dry bromine.

In a similar manner 5,5-dibromo-4-hydroxy-1,3,4-trimethylhydrouracil[2] and 1-benzyl-5,5-dibromo-4-hydroxy-4-methylhydrouracil[3] also form the mono-brominated uracils when refluxed with absolute alcohol.

Bremer[4] found that when the bromohydroxy derivative of 1,4,5-trimethyluracil was refluxed with absolute alcohol or heated by itself at 130° an unsaturated compound was formed, but in this case the unsaturation was caused by the elimination of a molecule of water. Kircher[5] found the same to be true with the bromohydroxy compound of 4,5-dimethyluracil when this compound was heated at 105°. Since both of these workers assume that the bromine atom of the added hypobromous acid is on the 4-carbon atom and the hydroxy group on the 5-carbon atom, they conclude that the molecule of water is split off with the formation of a methylene group on the 5-carbon atom. Thus, in the case of the 4,5-dimethyl-

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[1]Behrend, Ann., 236, 58 (1886).

[2]Hagen, loc. cit., p. 244. [3]Hoebel, loc. cit., p. 265.

[4]Bremer, loc. cit., p. 200.

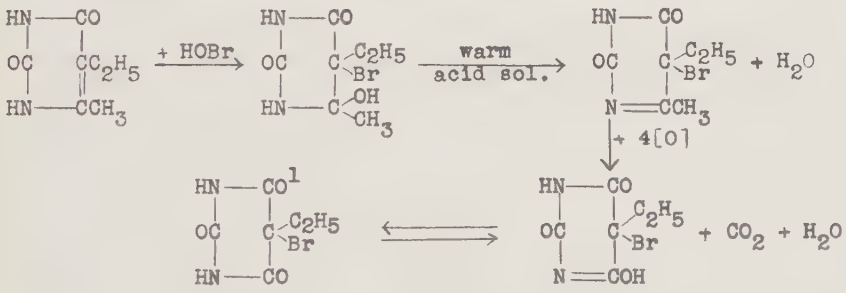
[5]Kircher, loc. cit., p. 310.

uracil derivative the reaction would be as follows:

$$NH.CO.NH.CBr(CH_3).C(OH)(CH_3).CO \xrightarrow[105^o]{\text{heat}}$$

$$NH.CO.NH.CBr(CH_3).C(:CH_2).CO + H_2O$$

Here, again, the 4-methyl-5-ethyluracil derivative does not seem to follow the course of reaction suggested by Kircher for his 4,5-dimethyluracil derivative. When the bromohydroxy derivative of 4-methyl-5-ethyluracil (already proven to be 4-methyl-4-hydroxy-5-bromo-5-ethylhydrouracil) is refluxed with absolute alcohol the same mono-brominated 4-methyl-5-ethyluracil is formed that was obtained by treating the uracil with dry bromine. The same mono-brominated uracil is also obtained when the bromohydroxyhydrouracil is warmed on a steam bath in an acidified water solution. When this brominated 4-methyl-5-ethyluracil, obtained by any of these methods, is oxidized with red fuming nitric acid bromoethylbarbituric acid is again formed. Thus the bromine atom in the mono-brominated 4-methyl-5-ethyluracil must be on the 5-carbon atom. To summarize by means of equations, the following is probably the course taken by the reactions described above:



The fact, then, that bromoethylbarbituric acid is formed by the oxidation with red fuming nitric acid from the mono-brominated 4-methyl-5-ethyluracil (prepared either by the bromination with dry bromine or by the dehydration of the bromohydroxyhydrouracil) as well as from the bromohydroxy 4-methyl-5-ethylhydro-

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[1] It is somewhat surprising that the ethyl group in the bromoethylbarbituric acid is not attacked by the red fuming nitric acid; but when bromoethylbarbituric acid, prepared by another method, was subjected to the experimental conditions used in the oxidation of the brominated uracil, the bromoethylbarbituric acid was recovered almost quantitatively.

uracil proves that the bromine atom in these compounds is situated on the 5-carbon atom. The question of the position of the double bond in the 4-methyl-5-bromo-5-ethyluracil molecule, however, is still to be considered. This question will be discussed in the next section.

4. Dibromohydroxy-4-methyl-5-ethylhydrouracil. That the mono-brominated 4-methyl-5-ethyluracil, formed either by the bromination of 4-methyl-5-ethyluracil with dry bromine or by the elimination of a molecule of water from the bromohydroxy 4-methyl-5-ethylhydrouracil, is an unsaturated compound is indicated by the fact that the compound when treated with bromine water absorbs a molecule of hypobromous acid. The following facts are offered as arguments confirming the assumption already made in the structural formula above, namely, that the double bond causing the unsaturation in the 4-methyl-5-bromo-5-ethyluracil molecule is situated between the 3-nitrogen atom and the 4-carbon atom.

a. 4-Methyl-5-bromo-5-ethyluracil absorbs hypobromous acid at a relatively slow rate. When 4-methyl-5-ethyluracil is suspended in water and bromine added, the addition at the double bond takes place as rapidly as the bromine goes into solution; so that the solution at no time has the color of bromine water before an equimolar quantity of bromine has been added. On the other hand, when 4-methyl-5-bromo-5-ethyluracil is suspended in water and bromine added, the solution takes on the color of bromine water and it is only after vigorous stirring that this color disappears.

b. The dibromohydroxy 4-methyl-5-ethylhydrouracil formed by the above reaction is quite unstable. When warmed with water it reverts in part to the original 4-methyl-5-bromo-5-ethyluracil; the other part being further oxidized, resulting in the formation of a syrup similar to that obtained by other oxidizing agents to be discussed later. A reaction product obtained from 4-methyl-5-bromo-5-ethyluracil and hypobromous acid would be expected to be unstable if the addition takes place according to the following equation:

$$\underline{NH.CO.N{:}C(CH_3).CBr(C_2H_5).CO} + HOBr \longrightarrow$$

$$\underline{NH.CO.NBr.C(OH)(CH_3).CBr(C_2H_5).CO}$$

c. The dibromohydroxy 4-methyl-5-ethylhydrouracil liberates iodine instantaneously when treated with potassium iodide in a slightly alkaline solution. If this mixture is immediately

acidified after thorough mixing and then titrated with sodium thiosulfate 67 per cent of the iodine expected to be liberated by one positive bromine atom is found to be present. If, however, the alkaline mixture is allowed to stand for two minutes, the free iodine is only 50 per cent of the expected amount. This would indicate the possibility that either the positive bromine liberated from the nitrogen atom does not exclusively oxidize the iodide ion to free iodine, but in part oxidizes the uracil, or that the iodine liberated in the alkaline solution oxidizes the uracil. The essential point indicated by the instantaneous liberation of iodine from the potassium iodide solution is that the second bromine atom introduced into the uracil molecule is quite reactive. This type of reactivity is, of course, to be expected if the bromine atom is situated on a nitrogen atom.

These facts, arguing in favor of the double bond between the 3-nitrogen atom and the 4-carbon atom, together with the formation of bromoethylbarbituric acid by the oxidation with nitric acid, indicate that the structure of the monobrominated 4-methyl-5-ethyluracil is the following:

$$\underline{NH.CO.N{:}C(CH_3).CBr(C_2H_5)CO.}$$

B. Behavior of 4-Methyl-5-Bromo-5-Ethyluracil

1. Toward Potassium Iodide. In contrast to the dibromohydroxy 4-methyl-5-ethylhydrouracil, 4-methyl-5-bromo-5-ethyluracil liberates iodine very slowly in a slightly alkaline solution. In neutral or acid solution the liberation of iodine from potassium iodide is no more rapid. After standing for about three hours in an acidified potassium iodide solution only 4 per cent of the iodine expected from an active bromine is present in the form of free iodine. When this acidified solution is allowed to stand for a few weeks a compound having the composition of 4-methyl-5-iodo-5-ethyluracil is formed. This same compound is formed when the mono-brominated uracil is allowed to stand for a few weeks in an acidified solution containing free iodine in place of potassium iodide. On the other hand, this compound is not formed when the original 4-methyl-5-ethyluracil is allowed to stand in a solution of free iodine. Instead, there is a formation of beautiful violet-colored needles that readily lose iodine. When an attempt was made to recrystallize these needles the original

4-methyl-5-ethyluracil was recovered from the brown iodine-colored solution. An analogous behavior with iodine was observed by Behrend and Hoffmann[1] in the case of 4-methyluracil.

2. Toward Hydrolysing Agents. When 4-methyl-5-bromo-5-ethyluracil is refluxed with water it gradually loses bromine and is converted almost quantitatively into a compound having the composition of 4-methyl-5-hydroxy-5-ethyluracil. The same compound is formed when the brominated uracil is refluxed in acid solution. Though a trace of a sweet-smelling oily substance that could not be identified was formed by this acid hydrolysis, the uracil ring, for the most part, remains unbroken. This same stability of the urcil ring toward acid hydrolysis was observed by Berhend[2] in the case of methyluracil.

In alkaline solution the 4-methyl-5-bromo-5-ethyluracil readily loses bromine. This reaction, however, is not instantaneous; for it was found that when the brominated uracil was dissolved in cold alkali and the solution immediately acidified, the brominated uracil precipitated unchanged. If, on the other hand, the alkaline solution was allowed to stand at room temperature for some time or warmed on the steam bath for a short while, the brominated uracil no longer precipitated when the solution was acidified. Instead, there was formed an emulsion from which a gel-like substance could be gathered on a filter. No definited crystalline compound could be isolated from this gel-like substance. A heavy precipitate that formed when silver nitrate was added to the filtrate already acidified with nitric acid indicated that the bromine was no longer attached to the uracil ring.

3. Toward Oxidizing Agents. The results of the oxidation of 4-methyl-5-bromo-5-ethyluracil with red fuming nitric acid has already been discussed. Oxidation with alkaline permanganate, however, needs to be considered at this point.

In alkaline permanganate solution the brominated 4-methyl-5-ethyluracil is readily oxidized. Although varying amounts of permanganate were used—amounts supplying one, two, three, or four atoms of oxygen per molecule of brominated uracil—the major oxidation product in all cases was a syrup which, upon thorough drying,

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[1] Berhend and Hoffmann, Ann., 253, 74 (1889).

[2] Ibid., 229, 24 (1885).

assumed the nature of an extremely hygroscopic resin. Small amounts of oxalic acid and oxaluric acid could be isolated and identified by means of their calcium and potassium salts respectively; but this is of little or no consequence. It only points out the well known fact that the uracil ring is easily broken by the oxidation with alkaline permanganate. What the formation of oxaluric acid does show is that the ethyl group on the 5-carbon atom is oxidized away in at least part of the brominated uracil. Whether or not this takes place after the ring has been ruptured or after the bromine atom has been removed by hydrolysis is impossible to say.

Metzner[1] reports that in one case when he oxidized some brominated 4-methyl-5-ethyluracil that was six months old with alkaline permanganate he was able to isolate a crystalline compound that greatly resembled bromoacetylurea with respect to its solubility in water and alcohol and its melting-decomposition point. Because of this resemblance he suggests the possibility of a migration of the bromine atom from the 5-carbon atom to the methyl group on the 4-carbon atom—a rearrangement analogous to the one observed by Hantzsch[2] in the case of brominated acetoacetic ethyl ester. If the compound isolated by Metzner was bromoactylurea, then the assumption that a rearrangement has taken place is, undoubtedly, correct; for only with the bromine atom on the side-chain methyl group is it possible to obtain bromoacetylurea from the mono-brominated 4-methyl-5-ethyluracil. Metzner suggests the following equation for this oxidation:

$$\underline{NH.CO.N{:}C(CH_2Br).CH(C_2H_5).CO} \rightarrow CH_2Br.CO.NH.CO.NH_2 + C_2H_5COCO_2K$$

The present author was anxious to procure the oxidation product described by Metzner in order to study it more closely, because his analyses for bromine and nitrogen varied considerably from the theoretical for bromoacetylurea. Thus he found 10.47 per cent nitrogen instead of the expected 15.46 per cent; and 47.80 per cent bromine instead of 44.20 per cent. It is peculiar that this compound—if this compound is bromoacetylurea with such a low degree of purity as indicated by the above analyses—should show such a great resemblance to pure bromoacetylurea in its

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[1]Metzner, loc. cit.

[2]Hantzsch, Ber., 27, 356, 3186 (1894).

melting-decomposition point.

The procedure used by Metzner[1] was carefully repeated a number of times, using brominated 4-methyl-5-ethyluracil seven months old and eight months old as the starting material. All these attempts, however, failed to produce the desired crystalline compound. The products of these reactions were found to be no different from those obtained when freshly prepared 4-methyl-5-bromo-5-ethyluracil was similarly oxidized.

Thus the questions whether the compound isolated by Metzner was bromoacetylurea and whether there is a migration of the bromine atom in the case of brominated 4-methyl-5-ethyluracil, are still open. This much, however, can be said: that if any migration of the bromine atom does occur this rearrangement is not complete after nine months. Proof for this may be found in the fact that brominated 4-methyl-5-ethyluracil, nine months old, when oxidized with red fuming nitric acid yields bromoethylbarbituric acid just as does the freshly prepared brominated uracil. It is true that the yield of crude bromoethylbarbituric acid in the case of the nine-month old compound was only about 30 per cent of the theoretical, but no better yield could be obtained from the freshly prepared compound. The identity in the percentage of these yields somewhat argues against the molecular rearrangement. Nevertheless, that Metzner was able to isolate a compound with such a high percentage of bromine (47.80 per cent) from the reaction mixture of the oxidation with alkaline permanganate remains a striking and unexplainable fact--a fact that is all the more striking because of the relative ease with which the bromine atom is lost by 4-methyl-5-bromo-5-ethyluracil in alkaline solution.

4. Toward Dimethylamine. 4-Methyl-5-bromo-5-ethyluracil may react with dimethylamine in two ways. First, it can react in a manner analogous to that observed by Behrend[2] between 4-methyl-5-bromouracil and ammonia, in which the bromine atom on the 5-carbon atom is replaced by the amino group. According to this the reaction between 4-methyl-5-bromo-5-ethyluracil and dimethylamine would be as follows:

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[1]Metzner, loc. cit.

[2]Behrend, Ann., 231, 250 (1885).

$$NH.CO.N{:}C(CH_3).CBr(C_2H_5).CO + 2HN(CH_3)_2 \longrightarrow$$
$$NH.CO.N{:}C(CH_3).C[N(CH_3)_2](C_2H_5).CO + [H_2N(CH_3)_2]Br$$

The other possible reaction between these two compounds would be the formation of a dimethylamine salt similar to the manner in which 5,5-dimbromobarbituric acid forms salts with primary and secondary amines.[1] Thus dibromobarbituric acid reacts as follows:

$$NH.CO.NH.CO.CBr_2.CO + 2H_2N(CH_3) \longrightarrow$$
$$NH.CO.NH.CO.CBr{:}CO[NH_3(CH_3)] + (CH_3)NHBr$$

If 4-methyl-5-bromo-5-ethyluracil reacts with dimethylamine in a similar manner the salt formation would take place according to the following equation:

$$NH.CO.N{:}C(CH_3).CBr(C_2H_5).CO + 2HN(CH_3)_2 \longrightarrow$$
$$NH.CO.N{:}C(CH_3).C(C_2H_5){:}CO\,[NH_2(CH_3)_2] + (CH_3)_2NBr$$

Fortunately, it is quite easy to distinguish between the compounds formed by these two types of reactions. It is a characteristic of the amine salts that they readily liberate the amines when treated with alkali, even in the cold. On the other hand, this is not the case with compounds requiring a splitting of a carbon to nitrogen linkage. When the dimethylamino compound obtained from the reaction between 4-methyl-5-bromo-5-ethyluracil and dimethylamine was subjected to steam distillation in alkaline solution no dimethylamine was liberated. Thus the compound must be the 4-methyl-5-dimethylamino-5-ethyluracil given by the first equation above, and not the dimethylamine salt given by the last equation.

C. Nitrogen Analyses

Before concluding this discussion attention must be drawn to the fact that Pregl's micro-Dumas method for nitrogen analysis yields consistently low results for the compounds encountered in this work. Similar results have been reported by Milner and Sherman[2] for some closely related compounds, as, for

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[1] Cope, Jour. Am. Chem. Soc., 54, 1250 (1932).

[2] Milner and Sherman, Ind. and Eng. Chem., (anal. ed), 8, 332 (1936).

example, 5-bromouracil and cytosine. Most of the compounds here investigated analyzed from 0.7 to 0.9 per cent low when Pregl's method was followed exactly. When a much hotter flame than the one suggested by Pregl was used for the burning, or a little potassium chlorate was mixed with the sample, this error could be reduced to about 0.4 or 0.5 per cent. When the micro-Kjeldahl method as described by Pregl was used, satisfactory results were obtained.

Although the results of the nitrogen analyses by the micro-Dumas method were found to be consistently low they will, because of this very fact, be recorded in their proper places in the experimental part of this paper.

III. EXPERIMENTAL PART

4-Methyl-5-ethyluracil, the main starting material for the experimental work reported here, was prepared according to the method of Lowe[1] as described in detail by Terre.[2]

1. 4-Methyl-5-bromo-5-ethyluracil,

$$NH.CO.N{:}C(CH_3).CBr(C_2H_5).CO.$$

The method first employed in the preparation of 4-methyl-5-bromo-5-ethyluracil was that described by Metzner[3] in which he treated 4-methyl-5-ethyluracil suspended in carbon disulfide with dry bromine. This method was found to be quite satisfactory when commercial bromine was used as the brominating agent, but completely unsatisfactory when C. P. bromine was used. Incomplete bromination was always encountered when C.P. bromine was used. The same was frequently found to be true, but in a lesser degree, in the case of commercial bromine, even when the mixture was agitated on a mechanical shaker for 18-20 hours.

Using absolute alcohol as a recrystallizing agent Metzner found it quite difficult to separate the brominated compound from the non-brominated. The author found the use of an acetone-water mixture to be a more effective means of separating these two compounds—three parts of acetone to one part of water being used. The crude bromination product was dissolved in the least possible amount of the hot acetone-water mixture. Then, by passing a rapid stream of air over the surface of this solution most of the acetone was evaporated. Long before the major portion of the acetone had been evaporated a copious precipitate of the brominated 4-methyl-5-ethyluracil, in the form of glistening white tablets, had separated. Since the non-brominated uracil is more soluble in water than the brominated compound, more of the former stays in the residual solution than of the latter. Thus by repeated re-

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[1] Lowe, Unpublished Work.

[2] Terre, Master's Dissertation, University of Chicago, 1932.

[3] Metzner, loc. cit.

crystallizations a pure brominated compound is eventually obtained.

Using this method of recrystallization, but otherwise following the procedure described by Metzner, a yield of from 70 to 80 per cent of the theoretical can be consistently obtained when commercial bromine is used for the bromination. If C.P. bromine is used, however, this yield drops to about 20 per cent.

The above method of bromination was eventually discarded in favor of a method that was less time consuming and resulted in an almost quantitative yield of the same 4-methyl-5-bromo-5-ethyluracil. Before dropping the procedure it was ascertained that the difference in the reactivity of commercial bromine and of C.P. bromine was due to chlorine present in commercial bromine as an impurity (about 0.5 per cent). As has already been pointed out above, it was found that when C.P. bromine was contaminated with chlorine to the extent of 0.5 per cent and so used in the procedure described by Metzner the results were identical with those obtained when commercial bromine was used, that is, there was a violent reactivity when the bromine was first added to the uracil suspended in carbon disulfide, a vigorous evolution of hydrogen halide fumes, a rather rapid settling of the uracil to the bottom of the container, together with a fair yield of the brominated compound—none of which were observed in the case of C.P. bromine.

Before it was definitely known that chlorine was the cause of the difference in the behavior of commercial bromine and C.P. bromine experiments were carried out in which other catalysts or halogen "carriers" were added to the C.P. bromine used for the bromination. These catalysts were iodine, ferric bromide, aluminum chloride and a few drops of water. None of these, however, caused the violent reactivity observed in the case of commercial bromine. In all cases, except the one in which the trace of moisture was added, there was a much more noticeable evolution of hydrogen bromide fumes than in the case where C.P. bromine alone was used. In all cases, especially in the case of ferric bromide and the trace of moisture, did the suspended uracil settle to the bottom of the container rather rapidly as compared to when C.P. bromine alone was used. Furthermore, all of these experiments yielded the same white glistening leaflets of 4-methyl-5-bromo-5-ethyluracil. The yield in all cases exceeded that in which C.P. bromine alone was used, in fact, the presence of ferric bromide and of the

trace of moisture produced a slightly higher yield than did the presence of chlorine.

The pure compound obtained in the above experiments decomposed at 249° when the oil bath containing the melting-point tube was heated at the rate of 4° per minute.[1] Analyses for nitrogen,[2] carbon and hydrogen gave the following results:

Calculated for $C_7H_9O_2N_2Br$: N, 12.02%; c, 36.02%; h, 3.86%

Found : N(Dumas), 11.15%, 11.13%, 11.22%

N(Kjeldahl), 11.84%, 11.91%

C, 36.19%; H, 3.92%

*Result obtained by Mr. Kurt Eder, a professional micro-analyst.

As stated above, this same 4-methyl-5-bromo-5-ethyluracil can be obtained with greater ease and with better yields by the following method. Finely pulverized 4-methyl-5-ethyluracil (3.1 g.) was thoroughly mixed with 20 cc. of water until a paste resulted. Bromine[3] was slowly added with vigorous stirring. The bromine was absorbed as rapidly as it went into solution. For that reason the solution did not assume the color of bromine until 3.3 g., 0.1 g. over the theoretical quantity of bromine, had been added. The bromine color now persevered even after thorough stirring. A rapid stream of air was passed over the surface of the reaction mixture until complete decolorization showed that the excess bromine had been removed. At no time during the addition of the bromine was the solution free of solid, and now that the excess bromine had been removed the solid had the appearance of a finely divided white flour-like substance. This mixture was placed on a steam bath and heated with intermittent stirring. Even now the solid did not dissolve completely, but gradually changed from its powder-like form to beautiful glistening white leaflets. After about one-half hour this change seemed to be complete. The mixture was cooled in an ice bath, the solid gath-

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[1]The decomposition points of this compound and other compounds here studied vary considerably with the rate with which the temperature is raised. Thus the above compound decomposes at 253° when the temperature is raised at the rate of 6° per minute.

[2]The results of the nitrogen analyses by the micro-Dumas method will be designated by N(Dumas), those by the micro-Kjeldahl method by N(Kjeldahl). Cf. p. 16.

[3]Hence C.P. bromine was used unless otherwise specified.

ered on a filter and washed three times with ice-cold water. Even without recrystallization this solid, weighing 4.3 g., decomposed at 249°. This, plus 0.2 g. recovered from the filtrate upon evaporation by means of a stream of air, gave a total of 4.5 g., a yield of 96 per cent. Mixtures of this compound and that obtained from the reaction with dry bromine also decomposed at 249°. The nitrogen content by the micro-Dumas method was 11.30 per cent, in agreement with the brominated 4-methyl-5-ethyluracil formed by the reaction with dry bromine.

2. 4-Methyl-4-hydroxy-5-bromo-5-ethylhydrouracil,

$$\underline{NH.CO.NH.C(OH)(CH_3).CBr(C_2H_5).CO}$$

Finely pulverized 4-methyl-5-ethyluracil (1.5 g.) was thoroughly mixed with 15 cc. of water and treated with bromine in the same manner as described in the previous experiment. This time, however, after the excess bromine had been removed the mixture was not heated on the steam bath. Instead, the white flour-like solid was gathered on a filter after the mixture had been chilled. The solid was washed three times with ice-cold water. The amount of solid obtained without working up the filtrate was 2.1 g., a yield of 84 per cent. When heated in a melting point tube the solid moistened at 150° and, as the temperature was gradually raised, appeared to become dry again. It decomposed at 246-7°. When dissolved in a hot acetone-water mixture (3:1) the compound again precipitated in the form of a white powder-like solid when the acetone was evaporated by a stream of air. The decomposition point of the compound was still the same and the softening at 150° was again observed. Nitrogen analyses gave the following results:

Calculated for $C_7H_{11}O_3N_2Br$: N, 11.16%

Found : N(Dumas), 10.63%

N(Kjeldahl), 11.30%

To see whether warming on the steam bath with water alone would cause this 4-methyl-4-hydroxy-5-bromo-5-ethylhydrouracil to lose a molecule of water, thus converting it to the 4-methyl-5-bromo-5-ethyluracil, 0.5 g. of the bromohydroxy compound was added to 6 cc. of water and heated for 40 minutes on a steam bath. The mixture was then cooled in an ice bath and the solid gathered on a filter. The 0.42 g. of solid obtained still had the appear-

ance of a finely divided powder and in a melting point tube still softened at 150° and decomposed at 246-7°. Thus the compound had undergone no change.

The above 0.42 g. was now added to 5 cc. of water and to this was added five drops of concentrated hydrochloric acid. When this mixture was heated on a steam bath the powder-like solid gradually went into solution and beautiful glistening leaflets began to separate out. When, after one-half hour, the change in the solid seemed complete the mixture was cooled, filtered and the solid washed with cold water. The 0.25 g. solid recovered decomposed at 249° both when heated alone in a melting point tube or when mixed with 4-methyl-5-bromo-5-ethyluracil obtained from the reaction with dry bromine.

These same glistening white leaflets, decomposing at 249°, were also obtained when 4-methyl-4-hydroxy-5-bromo-5-ethylhydrouracil was refluxed with absolute alcohol for one-half hour.

3. 3,5-Dibromo-4-methyl-4-hydroxy-5-ethylhydrouracil,

$$\underline{NH.CO.NBr.C(OH)(CH_3).CBr(C_2H_5).CO}$$

a. Preparation. Finely pulverized 4-methyl-5-bromo-5-ethyluracil (0.58 g.) was thoroughly mixed with water. Bromine was added in small portions with vigorous stirring. As the bromine went into solution the mixture assumed the color of bromine water, but as the stirring was continued this color again disappeared. It was only after a little more than 0.4 g. (equimolar quantity) of bromine had been added that the bromine color persevered even after thorough stirring. When about two-thirds of the required amount of bromine had been added about two-thirds of the solid seemed to have gone into solution. At this point a solid began to deposit at the surface of the beaker scratched by the stirring rod. The quantity of this finely divided precipitate increased rapidly as the rest of the bromine was added. After adding a slight excess of bromine the mixture was thoroughly stirred and then allowed to stand for 15 minutes. The excess bromine was removed by means of a rapid stream of air. The now colorless solution containing the white precipitate was chilled in an ice-salt bath, the solid gathered on a filter and then washed three times with ice-cold water. From the decrease in the amount of solid when the latter was washed with cold water it was apparent that

the solid was quite soluble in cold water. Only a 0.6 g. yield was obtained instead of the theoretical 0.82 g. to be expected from a quantitative absorption of a molecule of hypobromous acid. When dried the white solid gradually assumed a light yellow color. When heated in a melting point tube it softened at 140°; at 160° it was about half solid and half liquid and quite a vigorous evolution of gas set in; at a higher temperature it gradually turned black. Nitrogen analyses for the unrecrystallized powder-like solid gave the following results:

Calculated for $C_7H_{12}O_4N_2Br_2$: N, 8.50%

Found : N(Dumas), 7.71%, 7.69%

N(Kjeldahl), 8.51%

4-Methyl-5-bromo-5-ethyluracil prepared either by the reaction with dry bromine or by the dehydration of the bromohydroxy compound yielded identical results in the above reaction.

b. Reversion of the dibromo compound to the momobrominated uracil. When an attempt was made to recrystallize the above dibromo compound from an acetone-water mixture, glistening white leaflets were obtained that decomposed at 249° and yielded 11.40 per cent nitrogen by the micro-Dumas method. This, together with the analyses given above for the dibromo compound, indicates that a molecule of hypobromous acid was absorbed by the 4-methyl-5-bromo-5-ethyluracil to form a dibromo compound of the composition $C_7H_{12}O_4N_2Br_2$, and that subsequently the latter reverted to the original 4-methyl-5-bromo-5-ethyluracil in the recrystallization medium. The same reversion was found to take place when the dibromo compound was heated with water on a steam bath.

The dibromo compound (0.1 g.) was heated for two hours on a steam bath with 5 cc. of water. At first all of the solid went into solution, but when the solution had been evaporated to 1 cc. a solid had again precipitated. The mixture was chilled and the solid gathered on a small filter and washed with cold water. About 0.05 g. of glistening white leaflets were obtained that decomposed at 248°. This compound, without doubt, was 4-methyl-5-bromo-5-ethlyuracil. The filtrate when evaporated left a residue in the form of a gummy syrup that could not be made to crystallize. A similar syrup was obtained by the oxidation of 4-methyl-5-bromo-5-ethyluracil with potassium permanganate and chromic acid.

c. Behavior of the dibromo compound toward potassium iodide. When 0.1978 g. of 3,5-dibromo-4-methyl-4-hydroxy-5-ethylhydrouracil (0.6 millimols) was dissolved in 20 cc. of water and an excess of potassium iodide added, there was no instantaneous liberation of iodine. When, however, 2 cc. of 1.0 N potassium hydroxide was added to this mixture the solution immediately assumed the deep brown color of free iodine. The mixture was shaken vigorously for about ten seconds and then acidified with 5 cc. of 33 per cent acetic acid. The liberated iodine was titrated with 0.1100 N sodium thiosulfate, 7.31 cc. (0.804 milliequivalents) being required to decolorize the solution to which a little starch solution had been added as indicator. Had one of the bromine atoms of the dibromo compound acted as a positive bromine and liberated iodine quantitatively 1.200 milliequivalents of sodium thiosulfate would have been required for the titration. Thus only 67 per cent of the expected amount of iodine was liberated.

When 0.1165 g. of the dibromo compound (0.353 millimols) was treated in the same manner as described above except that the alkaline solution was shaken for two minutes instead of ten seconds before being acidified, only 0.355 milliequivalents of sodium thiosalfate was required for the titration. Thus only 50 per cent of the expected amount of free iodine was present at the time of the titration.

The dibromo compound was found to liberate iodine but very slowly in an acidified solution of potassium iodide.

4. 4-Methyl-5-iodo-5-ethyluracil,

$$NH.CO.N{:}C(CH_3).CI(C_2H_5).CO$$

4-Methyl-5-bromo-5-ethyluracil (0.1 g.) was dissolved in about 20 cc. of an acetone-water (3:1) mixture. An excess of potassium iodide and a few drops of acetic acid were added to this solution. This mixture which was colorless at first soon turned yellow. This color gradually deepened until after about three hours it was reddish brown from the iodine liberated. Reduction with 0.1100 N sodium thiosulfate, however, indicated that the iodine liberated was only about 4 per cent of that to be expected from an active bromine atom. In neutral or alkaline solution iodine was liberated with no greater rapidity.

When an acidified solution analogous to the one described above was allowed to stand for three weeks in a closed container

and then evaporated down to 3 cc. by means of a stream of air a solid precipitated. This solid when recrystallized from an acetone-water mixture formed glistening yellow leaflets that in a melting point tube darkened at 244°, giving off a purple vapor. With further elevation of the temperature the solid gradually decomposed to a black liquid.

This same compound was formed when free iodine was added to the above acidified solution in place of the potassium iodide. Nitrogen analyses indicate that this compound probably is 4-methyl-5-iodo-5-ethyluracil.

Calculated for $C_7H_9O_2N_2I$: N, 10.00%

Found : N(Dumas), 9.65%, 9.66%

N(Kjeldahl), 10.15%

5. Hydrolysis of 4-Methyl-5-bromo-5-ethyluracil.

a. In neutral solution. 4-Methyl-5-bromo-5-ethyluracil (0.7 g.) was refluxed with 75 cc. of water for twenty-one hours. After this time the solution had assumed a light yellowish-brown color and was acid to litmus. The solution was evaporated down to 5 cc. and then cooled in an ice bath. A heavy precipitate of fine needles having the appearance of glass wool was formed. This, when collected on a filter, washed with cold water and dried, weighed 0.50 g. The theoretical yield for the formation of 4-methyl-5-hydroxy-5-ethyluracil is 0.51 g. This needle-like solid, after being recrystallized from hot water, melted at 215-6° with slight decomposition. The filtrate of the original solution when acidified with nitric acid gave a heavy precipitate with silver nitrate.

Nitrogen analysis showed that the compound formed above is probably 4-methyl-5-hydroxy-5-ethyluracil,

$$\underline{NH.CO.N{:}C(CH_3).C(OH)(C_2H_5).CO}$$

Calculated for $C_7H_{10}O_3N_2$: N, 16.47%

Found : N(Dumas), 15.70%, 15.67%

N(Kjeldahl), 16.34%, 16.41%

b. In acid solution. 4-Methyl-5-bromo-5-ethyluracil (0.2 g.) was refluxed for eighteen hours with 20 cc. of 6 N sulfuric acid, the solid gradually going into solution. After this time the solution had assumed a dark brown color and had a sweet

odor. No precipitate was formed when the mixture was cooled in an ice bath. The solution was extracted with ether about three or four times. When these ether extracts were evaporated the residue consisted of a thin film of a sweet-smelling oil and a few fine needle-like crystals similar to the ones described above. The trace of sweet-smelling oil could not be identified.

The original acid solution was neutralized with sodium hydroxide and evaporated to dryness on a steam bath. The solid was extracted three times with small portions of hot alcohol. These extracts were evaporated down to about 3 cc. and chilled. About 0.1 g. of fine needles separated out. These when recrystallized from hot water melted with slight decomposition of 215-6°, and had the appearance of glass wool just like the compound obtained by refluxing the brominated 4-methyl-5-ethyluracil with water.

c. In alkaline solution. A small amount of 4-methyl-5-bromo-5-ethyluracil was dissolved in about 1 cc. of normal potassium hydroxide. The solution was immediately acidified with nitric acid. The glistening white leaflets of the brominated uracil precipiated. Having collected the solid on a filter, the filtrate gave no precipitate when silver nitrate was added.

On the other hand, when an alkaline solution containing some of the brominated uracil was warmed on a steam bath for a few hours and was then acidified with nitric acid the glistening leaflets did not precipitate. Instead, there was formed an emulsion which when filtered left a gel-like residue on the filter. This amorphous material would not crystallize and so could not be identified. The filtrate yielded a heavy precipitate when silver nitrate was added. Results analogous to these were obtained when the alkaline solution was allowed to stand for a few days at room temperature instead of warming it on the steam bath for a few hours.

6. Oxidation of 4-Methyl-5-bromo-5-ethyluracil.

a. With nitric acid. After several other attempts had been made, the best results for the oxidation of 4-methyl-5-bromo-5-ethyluracil with nitric acid were obtained by the following method. Brominated 4-methyl-5-ethyluracil (2.3 g.) was added in small portions to 10 cc. of red fuming nitric acid. The uracil dissolved with considerable evolution of heat. When all the uracil had been added the mixture was placed on a steam bath and heated until it had evaporated to dryness. Next, 10 cc. more of

red fuming nitric acid was added and this again evaporated to dryness. The residue was a mixture of a solid and a syrup. To this mixture 5 cc. of water was added and then heated for 15 minutes on the steam bath. By this time both the syrup and the solid had gone into solution. When this solution was cooled in an ice bath considerable solid precipitated. This solid was gathered on a filter, washed with cold water and dried. It weighed 0.7 g. After five recrystallizations from hot water this compound melted with slight decomposition at 203-4°. Further recrystallization did not change this melting point. The crystals when allowed to form slowly had the appearance of small saw-edged daggers. The water solution of the compound was definitely acid towards litmus. It gave a strong positive Beilstein test. It liberated iodine instantaneously from a neutral potassium iodide solution. All of these properties, melting point, crystal structure, etc., were found to coincide with the properties of bromoethylbarbituric acid that had been prepared according to the method described by Conrad and Guthzeit.[1] A mixture of the oxidation product and bromoethylbarbituric acid also melted with slight decomposition at 203-4°. Analyses of the oxidation product gave the following results:

Calculated for $C_6H_7O_3N_2Br$: N, 11.91%; c, 30.64%; h, 2.98%

Found : N(Dumas), 11.00%, 11.11%

N(Kjeldahl), 12.04%, 12.02%

C, 30.68%; H, 3.07%

Thus this oxidation product is bromoethylbarbituric acid.

The above experiment was carried out with 4-methyl-5-bromo-5-ethyluracil that had been prepared by the dehydration of 4-methyl-4-hydroxy-5-bromo-5-ethylhydrouracil. The yield of the crude product was about 30 per cent. When 4-methyl-5-bromo-5-ethyluracil, prepared by treating 4-methyl-5-ethyluracil with dry bromine, was oxidized in the same manner the same yield of the same compound was obtained. This was found to be the case for both the freshly prepared brominated 4-methyl-5-ethyluracil as well as for the nine-month old compound. When 4-methyl-4-hydroxy-5-bromo-5-ethylhydrouracil was oxidized with red fuming nitric acid in a similar manner the same compound in a yield of

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[1] Conrad and Gurthzeit, Ber., 15, 2846 (1882).

40 per cent of the theoretical was obtained.

b. Oxidation with potassium permanganate. In the oxidation of 4-methyl-5-bromo-5-ethyluracil with potassium permanganate the method described by Metzner[1] was followed. Altogether nine oxidation reactions were carried out with potassium permanganate in the hope that the halogen-containing organic compound described by Metzner might be isolated. Brominated 4-methyl-5-ethyluracil seven months old, eight months old, as well as freshly prepared material was oxidized according to the method described by him. In other cases the amounts of permanganate used for the oxidation were varied so as to supply one, two, three or four atoms of oxygen per molecule of the uracil. In still another case the oxidation was started in a neutral solution, that is, the addition of alkali was omitted at the beginning of the experiment. All these efforts,however, were futile, for in all cases the major oxidation product was a syrup that with thorough drying in a vacuum desciccator over sulfuric acid formed a hygroscopic resin that could not be made to crystallize. The only oxidation products that could be isolated in small quantities and identified were oxalic acid, in the form of its calcium salt, and oxaluric acid, in the form of its potassium salt.[2]

c. Oxidation with chromic acid. When 4-methyl-5-bromo-5-ethyluracil was oxidized with chromic acid in a glacial acetic acid solution the main oxidation product was again a syrup.

7. 4-Methyl-5-dimethylamino-5-ethyluracil,

$$\underline{NH.CO.N:C(CH_3).C[N(CH_3)_2](C_2H_5).CO}$$

a. Preparation. 4-Methyl-5-dimethylamino-5-ethyluracil was prepared by a slightly modified form of the method described by Metzner.[3]

4-Methyl-5-bromo-5-ethyluracil (2.3 g. = 0.01 mol) was added to 10.5 g. (0.06 mol) of dimethylamine solution (26.4 per cent). This mixture was vigorously shaken in a stoppered flask until all of uracil had gone into solution. Considerable heat

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[1]Metzner, loc. cit.

[2]Behrend and Grünewald, Ann., 323, 186 (1902).

[3]Metzner, loc. cit.

was liberated and in about five minutes all of the uracil had dissolved. The solution which had assumed a light yellow color was set aside and allowed to stand at room temperature for four days. After this time the solution was evaporated to dryness by means of a stream of air. The solid residue was dissolved in the least possible amount of hot methyl alcohol. This solution was cooled in an ice-salt bath and the solid that precipitated gathered on a filter and washed with a small amount of ice-cold methyl alcohol. When dry this solid weighed 1.9 g. After two more recrystallizations from methyl alcohol it melted at 155-6°. Further recrystallization did not change this melting point. The pure compound weighed 1.0 g., representing a 50 per cent yield of the theoretical. Nitrogen analyses yielded the following results:

Calculated for $C_9H_{15}O_2N_3$: N, 21.32%

Found : N(Dumas), 20.57%, 20.42%

N(Kjeldahl), 21.39%, 21.15%

b. Proof that the dimethylamino compound is not a dimethylamine salt. The dimethylamino compound of 4-methyl-5-ethyluracil (2.437 mg.) was dissolved in 3 cc. of water and introduced into a micro-Kjeldahl distilling apparatus. After adding 6 cc. of 30 per cent potassium hydroxide solution, the mixture was subjected to steam distillation for four minutes; the distillate being collected in an acid solution containing 0.0738 milliequivalents of hydrochloric acid. For the back titration 0.0734 milliequivalents of sodium hydroxide were required. From this it is evident that no dimethylamine was liberated and, therefore, that the compound is not a salt of dimethylamine. Had it been a salt 0.0122 milliequivalents of dimethylamine would have been liberated by the distillation and only 0.0612 milliequivalents of base would have been required for the back titration.

SUMMARY

It has been established that the product of the bromination of 4-methyl-5-ethyluracil is 4-methyl-5-bromo-5-ethyluracil. The main proof offered for the structure of this compound is the formation of bromoethylbarbituric acid when the brominated uracil is oxidized with red fuming nitric acid. No evidence was found indicating a molecular rearrangement in this brominated uracil analogous to that of brominated acetoacetic ester, but neither can the possibility be rigorously excluded.

The reaction product of 4-methyl-5-bromo-5-ethyluracil and dimethylamine was found to be 4-methyl-5-dimethylamino-5-ethyluracil.

The following new compounds were prepared and their physical constants determined:

1. 4-methyl-5-iodo-5-ethyluracil,
2. 4-methyl-5-hydroxy-5-ethyluracil,
3. 4-methyl-4-hydroxy-5-bromo-5-ethylhydrouracil,
4. 3,5-dibromo-4-methyl-4-hydroxy-5-ethylhydrouracil.

In conclusion, the author wishes to express his indebtedness to the late Dr. Julius Stieglitz for suggesting the work here recorded; to Drs. Raymond W. Johnson and Morris S. Kharasch for their kind suggestions while the work was in progress; and to Dr. Frank R. Mayo for his helpful criticism in the writing of this report.